REMARKS/ARGUMENTS

Claims 1 and 39-46 remain pending in this application. Claims 2-38 have been canceled in a previous Amendment. Claims 39-46 have been withdrawn as the result of an earlier restriction requirement. In view of the Examiner's earlier restriction requirement, Applicants retain the right to present claims 39-46 in a divisional application.

In response to the Office Action of July 19, 2005, Applicant requests re-examination and reconsideration of this application for patent pursuant to *35 U.S.C. § 132*.

Double Patenting

Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 of copending Application No. 11/439,587. The Examiner asserts the instant Claim 1 of George *Jackowski et al.* discloses an isolated biopolymer marker consisting of SEQ ID NO:1.

Accordingly, a terminal disclaimer in compliance with *37 CFR 1.321(c)* has been filed. Applicant respectfully requests that the above-mentioned rejection now be withdrawn.

Rejections under 35 U.S.C. § 101

Claim 1 stands rejected under *35 U.S.C. § 101* because the claimed invention is not supported by either a specific, credible or a well-established utility. The Examiner notes Applicant's claim that the identification of bands 2 and 3 in Figure 1 of the drawings are indicative of SEQ ID NO:1 and based on the differential expression of the bands between samples from normal and disease-state patients are indicative of a link to at least one disease. The Examiner asserts, however, that: in Figure 1 of the drawings band 3 is not evident in Diabetes type I, and one disease sample of Insulin Resistance; Figure 1 of the instant drawings reveal that band 3 is evident in one disease sample of Insulin Resistance and two normal samples; Band 2 in Figure 1 of the drawings is not evident in any normal or disease samples. The Examiner concludes that the differential expression of SEQ ID NO: 1 is not evident and the data results are ambiguous. The Examiner maintains that the correlation with respect to a link to insulin is not exemplified or disclosed in the specification in a way that one of ordinary skill in the art could distinguish the differential expression in an insulin resistance subject versus that of a normal subject. The Examiner further asserts one of ordinary skill in the art would not be able to distinguish a credible and specific or well establish utility that SEQ ID NO: 1 is linked to insulin

resistance, and as a result, the specification does not identify a substantial, credible or well-established utility for sequence consisting of SEQ ID NO: 1.

Applicants respectfully disagree with the Examiner's assertions. Claim 1 of the instant application, as described in the specification of the originally filed application, relates to the utilization of mass spectrometry to elucidate particular biopolymer markers, SEQ ID NO:1, indicative of a disease state, specifically Insulin Resistance (see page 1, lines 5-12, page 46 lines 5-12, and Figures 1 and 3). Accordingly, Applicants have identified a substantial, credible and well-established utility for sequence consisting of SEQ ID NO: 1.

Applicants assert that SEQ ID NO:1 is useful for diagnosis and treatment of insulin resistance since it was found to evidence a link to insulin resistance (an "asserted" utility). This asserted utility is supported by data derived from the working examples (the gel shown in Figure 1 and the mass spectrometric graph shown in Figure 3), which shows that the claimed biopolymer marker is differentially expressed between insulin resistance/diabetes and patients determined to be normal with regard to insulin resistance and diabetes. Applicants' statement of an asserted utility also constitutes a specific and substantial utility that is supported by the specification as

originally filed (see page 1, lines 5-13; page 35, lines 14-18; page 46, lines 5-12; and Figures 1 and 3.

The Examiner states "However, in Figure I of the drawings reveal that band 3 is not evident in Diabetes type I, and one disease sample of Insulin Resistance. Figure 1 of the instant drawings reveals that band 3 is evident in one disease sample of Insulin Resistance and two normal samples. Band 2 in Figure 1 of the drawings is not evident in any normal or disease samples. Therefore the differential expression of SEQ ID NO: 1 is not evident and the data results are ambiguous." It is possible that the copy of Figure 1 submitted to the Examiner was not a clean copy. As a result, a cleaner copy of Figure 1 with a Declaration Under *37 C.F.R. § 1.132*, as originally filed, has been attached to this Amendment.

Figure 1 is a photograph of a tricine gel HiQ 1 (Elution) comparing Insulin Resistance verses Normal. Reading from the left, the gel pictured in Figure 1 has 10 lanes; lane 1 contains the low molecular weight standards; lane 2 contains a sample obtained from a Type I diabetes patient; lanes 3 and 4 contain samples obtained from insulin resistance patients; lanes 5 and 6 contain samples obtained from Type II diabetes patients; lanes 7-9 contain samples obtained from patients determined to be normal with regard to insulin resistance/diabetes and lane 10

contains the high molecular weight standard. Figure 1 shows Band 2 expression in both normal and diseased state patients (Insulin Resistance and Diabetes I/II). Although expression was observed in all samples, band intensity for samples corresponding to the normal patients (lanes 7-9) is higher when compared to the band intensity corresponding to patients known to have Insulin Resistance or Diabetes Type I/II (lanes 2-6). Figure 1 further shows Band 3 expression in diseased state patients (Insulin Resistance and Diabetes I/II, lanes (2-6) but not in samples from normal patients. Thus, a clear difference in up and down regulation of the marker can be determined.

In viewing the currently submitted, cleaner version of Figure 1, contrary to the Examiner's statement that Figure 1 reveals that Band 3 is not evident in Diabetes Type I and one disease IR sample, it is clear that Band 3 is evident in all five diseased-state patient samples. Moreover, in contrast to the Examiner's statement that Band 3 is evident in two normal samples, Figure 1 clearly shows that Band 3 is not evident in any of the lanes corresponding to normal samples. With regards to Band 2, it is clear from looking at the Figure Band 2 is evident both in normal and disease samples. These results indicate that the data results are not ambiguous and that the differential expression of SEQ ID NO:1 is evident.

The currently pending claims recite a biopolymer marker (SEQ ID NO:1) which evidences a link to insulin resistance. It is important to point out that the disease specific markers which result from the procedures of the instant invention are Inter alpha trypsin inhibitor having a molecular weight of about 1811 daltons and a sequence of SEQ ID NO:1, a molecular weight of about 1582 and a sequence of SEQ ID NO:2, and a molecular weight of about 1337 daltons and a sequence of SEQ ID NO:3 as described in the specification, page 46 lines 5-12.

The Examiner states that the differential expression of SEQ ID NO:1 is not evident and the data results are ambiguous. Evidence of the differential expression of SEQ ID NO:1 has been addressed and described in the arguments above. To clarify the Examiner's concern that the data seems to be ambiguous, Applicants point out that Band 3 corresponds to the sequence that is covers in the claims of the instant invention. In Examining Figure 1, it is clear that Band 3 is visualized in the lanes corresponding to the insulin resistance/diabetes patient samples (lanes 2-6) and not present in normal patients (lanes 7-9). Further analysis by mass spectrometry indicates Band 3 has molecular weight of 1811 and sequence ID of SEQ ID NO:1 (See Figure 3).

Although the figure box corresponding to Band 2 in Figure 1 indicates that Band 2 to be Inter alpha trypsin inhibitor, there are differences to that of Band 3. First, the distance the bands traveled on the gel are dissimilar. Band 2, visualized in disease state samples, is located at a higher position on the gel than that of band 3, suggesting that the bands may have changed as a result of the disease process. More importantly, the ion spectras and sequence identifications are different. As mentioned before, Band 2 corresponds to inter alpha trypsin inhibitor with an identified molecular weight of 1582 daltons and corresponding SEQ ID NO:2 and molecular weight of 1337 daltons and corresponding to sequence SEQ ID NO:3. The instant application claims a biopolymer marker of SEQ ID NO:1, which is different to that identified on Band 2, as evidenced by Figure 1, Band 3 and Figure 3.

When comparing Band #3, as shown in the gel of Figure 1, it is evident that the claimed biopolymer marker, inter-alpha trypsin inhibitor, is differentially expressed between a disease state (insulin resistance/diabetes) and normal controls. The differential expression of the inter-alpha trypsin inhibitor indicates that this protein may be linked to insulin resistance and/or diabetes, thus supporting the claims as currently pending. Further analysis by mass spectrometry indicated that

SEQ ID NO:1 was evident in disease state patient samples but not in normal patients.

In the search for specific biomarkers, proteins found to be differentially expressed between "disease" and "normal" are frequently identified as potential targets for diagnostics and/or therapeutics. It is common practice in proteomics to select potential disease markers by their differential expression between a disease and a non-disease state. .

As stated in the Response to Office Action of October 21, 2003, levels of plasma proteins, including the plasma protease inhibitor, inter-alpha inhibitor, can change in disease states (*Salier et al.* Biochemistry Journal 315:(Pt 1):1-9 1996;). Additionally, it has previously been shown that the levels of inter-alpha-trypsin inhibitor can fluctuate in disease and normal pathological events (*Odum et al.* Clin Chim Acta. 162(2):189-198 1987). Consequently, one of skill in the art would connect the differential expression of SEQ ID NO:1 with potential diagnostics and/or therapeutics for insulin resistance/diabetes and would immediately appreciate why Applicants regard the claimed isolated biopolymer, SEQ ID NO:1, as useful, indicating that the utility of the claimed SEQ ID NO:1 is well-established

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under *35 U.S.C. § 101* now be withdrawn.

Rejections under 35 U.S.C. § 112

Claim 1 further stands rejected under 35 USC 112, first paragraph. The Examiner asserts that since the claimed invention is not supported by either a specific, substantial, asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not known how to use the claimed invention. For the reasons as outlined above, Applicant has identified a specific, substantial, asserted utility or a well established utility. Having identified specific, substantial, asserted utility or a well established utility, one skilled in the art clearly would how to use the claimed invention.

Thus, Applicant requests that this rejection under *35 U.S.C. § 112*, first paragraph now be withdrawn.

SUMMARY

In light of the foregoing remarks and amendment to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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